Anesthesiology
1999; 91:1604–15

Changes in Electroencephalogram and Autonomic Cardiovascular Activity during Induction of Anesthesia with Sevoflurane Compared with Halothane in Children

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Background: **This study was design to assess clinical agitation, electroencephalogram (EEG) and autonomic cardiovascular activity changes in children during induction of anesthesia with sevoflurane compared with halothane using noninvasive recording of EEG, heart rate, and finger blood pressure.**

Methods: **Children aged 2–12 yr premedicated with midazolam were randomly assigned to one of three induction techniques: 7% sevoflurane in 100% O_2 (group $Sevo_{RAPID}$); 2%, 4%, 6%, and 7% sevoflurane in 100% O_2 (group $Sevo_{INCR}$); or 1%, 2%, 3%, and 3.5% halothane in 50% N_2O–50% O_2 (group $Halo_{N_2O}$). An additional group of children who received 7% sevoflurane in 50% N_2O–50% O_2 (group $Sevo_{N_2O}$) was enrolled after completion of the study. Induction was videotaped. EEG, heart rate, and finger blood pressure were continuously recorded during induction until 5 min after tracheal intubation and analyzed in frequency domain using spectral analysis.**

Results: **Agitation was more frequent when anesthesia was induced with 100% O_2 compared to the mixture of oxygen and nitrous oxide. No seizures were recorded in any group. In the four groups, induction of anesthesia was associated with an increase in EEG total spectral power and a shift toward the low-frequency bands. Sharp slow waves were present on EEG tracings of the three sevoflurane groups, whereas slow waves and fast rhythms (spindles) were observed in the halothane group. Sevoflurane induced a greater withdrawal of parasympathetic activity than halothane and a transient relative increase in sympathetic vascular tone at loss of eyelash reflex.**

Conclusions: **Agitation observed during sevoflurane induction was not associated with seizures. Sevoflurane induction induced a marked inhibition of parasympathetic control of heart rate. (Key words: Agitation; autonomic nervous system; pediatric anesthesia; spectral analysis.)**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 7A.

SEVOFLURANE has a pleasant, nonpungent odor with minimal respiratory irritability that makes it suitable for mask induction. Sevoflurane inductions have initially been performed by increments in inspiratory concentration, based on historical precedent with other volatile agents such as halothane. Because sevoflurane has a safer respiratory and cardiovascular profile than that of halothane,[1,2] high inspired concentrations can be used to speed up loss of consciousness and to reduce a child's distress scores.[3,4] However, agitation is not uncommon during induction of anesthesia with sevoflurane in children.[3,5] Agitation is usually observed after loss of consciousness and consists of uncoordinated movements associated with mild to severe body and limb hypertonia. However, no study has evaluated the electroencephalogram (EEG) changes that may occur during induction of anesthesia with sevoflurane in children. Case reports have described clinical seizure-like activity in children during induction of anesthesia with high-dose sevoflurane,[6,7] but EEG evidence of seizure has only been reported in one healthy child during anesthesia[8] and in epileptic children.[9] Such seizure-like activity has been

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Received from the Service d'Anesthésie-Réanimation, Hopital d'Enfants Armand Trousseau, Paris, France; Service de Neurologie Pédiatrique, Hopital Saint Vincent de Paul, Paris, France. Submitted for publication March 8, 1999. Accepted for publication August 2, 1999. Supported by a grant from Abbott Laboratories, Inc., Abbott Park, Illinois (Protocol W97-230). Presented in part at the annual meeting of the American Society of Anesthesiologists, Orlando, Florida, October 17–21, 1998.

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described during enflurane anesthesia[10–13] but not with halothane, even in epileptic children.[14]

In addition to behavioral changes, the early induction phase is associated with an increase in heart rate (HR) and systolic blood pressure (SBP) in approximately 30–50% of pediatric patients.[3,15,16] This may result from changes in autonomic cardiovascular activity despite no sympathetic activation having been described in healthy volunteers anesthetized with sevoflurane.[17] The autonomic cardiovascular activity may be evaluated noninvasively using continuous blood pressure (BP) and HR recordings.[18,19] Sympathetic and parasympathetic autonomic inputs into the sinoatrial node contribute to the HR power spectrum in well-determined frequency ranges. Indeed, low-frequency (LF) HR baroreflex-mediated fluctuations reflect the interplay of parasympathetic and sympathetic tone,[20,21] whereas fluctuations of high frequency (HF) coinciding with the respiratory frequency are mainly caused by parasympathetic drive. With regard to BP, the LF oscillations reflect the vascular sympathetic modulation,[22] whereas HF fluctuations proceed from changes in cardiac output likely *via* respiratory induced changes in HR and ventricular filling.[23]

This study was designed to evaluate EEG tracings and autonomic cardiovascular activity changes in children during induction of anesthesia with sevoflurane administered either by gradual increments or at a high concentration using halothane as the reference induction gas.

Materials and Methods

Patients and Study Design

The study was approved by the Ethics Committee (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Saint-Antoine, France), and written informed consent was obtained from parents. Children with American Society of Anesthesiologists physical status I who were aged 2–12 yr and were scheduled for elective tonsillectomy were entered onto the study. They were randomly assigned to one of three induction techniques: rapid induction with 7% sevoflurane in 100% O_2 (group $Sevo_{RAPID}$); incremental induction with 2%, 4%, 6%, and 7% sevoflurane every 5 breaths in 100% O_2 (group $Sevo_{INCR}$); incremental induction with 1%, 2%, 3%, and 3.5% halothane every 5 breaths in a mixture of oxygen and nitrous oxide (50:50; group $Halo_{N_2O}$). All children were premedicated 15 min before induction with 0.5 mg/kg midazolam administered rectally (maximum dose, 10 mg). Children received no drug other than the volatile agent until completion of the study, *i.e.*, 5 min after placement of the tracheal tube. Mask induction was performed using an open circuit with a non-rebreathing valve at high fresh-gas flow (8 l/min) by the same two unblinded investigators (M. C. D. and V. P.). Expired gases and oxygen saturation were continuously recorded (Capnomac Ultima; Datex Instrument Corporation, Helsinki, Finland). Time to loss of eyelash reflex and time to obtain central pupils were recorded. In addition, the degree of airway obstruction and time to insert an oral airway, if required, were recorded. Ventilation was manually assisted before tracheal intubation at a rate close to 20 breaths/min. Tracheal intubation was performed using a RAE cuffed tracheal tube after placement of the intravenous line, and just after visualization of pupils in central position. After placement of the tracheal tube, the lungs were mechanically ventilated with a tidal volume of 10 ml/kg at a rate of 20 breaths/min (Servo 900D; Siemens, Göteborg, Sweden), inspired concentration was reduced to obtain 1 minimum alveolar concentration (MAC) of alveolar gas according to age,[24,25] and this expired concentration was maintained for 5 min. Surgery started after completion of the study.

Electroencephalogram and hemodynamic data (see Analysis of Data) were continuously recorded in awake children before anesthesia and during induction until 5 min after tracheal intubation. All data were analyzed at baseline before anesthesia, at time of loss of eyelash reflex, just before tracheal intubation, and 5 min after tracheal intubation when expired anesthetic concentration was equal to 1 MAC. After completion of the study, halothane was discontinued in the $Halo_{N_2O}$ group, and anesthesia was maintained with sevoflurane in 50% N_2O in all children. Recordings were continued for an additional 5 min after switching from halothane to sevoflurane (1 MAC expired concentration) in the last six patients allocated to the $Halo_{N_2O}$ group.

The induction period until 5 min after placement of the tracheal tube was videotaped and reviewed by a blinded independent pediatric neurologist (M. L. M.) to assess clinical signs and duration of agitation phase. Only involuntary movements unrelated to mask placement or venous puncture and occurring before the time of tracheal intubation were analyzed. The presence of involuntary movements was scored on a three-point scale: 0 = absent, 1 = localized to upper body; and 2 = generalized. Time at the beginning and end of the agitation phase was recorded.

Additional Study Group

An additional group of 10 patients was later enrolled after completion of the study in an open-label, nonrandomized arm. Patients in this group ($Sevo_{N_2O}$) received 7% sevoflurane in a mixture of oxygen and nitrous oxide (50:50). These patients were subjected to similar inclusion criteria, were premedicated with midazolam, and the same EEG and hemodynamic data were recorded. This additional group was deemed necessary after completion of the study and analysis of data because EEG and cardiovascular profiles differed between the halothane group and the two sevoflurane groups. In the initial study design, nitrous oxide was used in the halothane group because it corresponded to an established clinical practice, whereas it was omitted in the two sevoflurane groups to evaluate only the effects of sevoflurane.

Analysis of EEG Data

Electroencephalogram was continuously recorded by an experienced EEG technician on 16 channels using a rubber helmet containing 20 cream-filled cup electrodes placed according to the 10-20 international system (Micromed, Merignac, France). The helmet has a chin strap designed to keep the electrodes snug on the scalp. The EEG signal was acquired on a microcomputer (Compaq, Houston, TX) using the Brain-Quick program (system II, Micromed, Merignac, France) and stored on hard disk. Bandpass filters were set at 0.5–30 Hz, and amplifier sensitivity was 200 μV.[26] EEG was analyzed in the frequency domain.[27] Spectral analysis of EEG signal was performed using fast Fourier transformation (Acqknowledge v3.25; Biopac Systems, Inc., Santa Barbara, CA) on 5.12-s epochs[28] from the C3–P3 leads. The following parameters were calculated[27]: total spectral power (TSP), defined as the area under the curve of the spectrum (μV^2); spectral edge frequency 95, defined as the frequency below which 95% of the EEG power is located; and median power frequency, defined as the frequency below which 50% of the EEG power is located. Spectral bands of 0–4 Hz (δ), 4–8 Hz (θ), 8–13 Hz (α), and 13–30 Hz (β) were analyzed, and the power of the spectral bands was calculated and expressed as percentage of TSP. The δ ratio (ratio of the power in the 8–30 Hz band to power in the 0–4 Hz band) was calculated. All EEGs were reviewed by an independent blinded pediatric neurologist to assess whether seizure-like activity was present.

Analysis of Autonomic Cardiovascular Activity

Electrocardiograph measurements were taken with disposable electrodes attached to the thorax and placed to provide clear R waves and were connected to a Datex cardiocap II monitor (Datex Instrumentation Corp). Finger arterial pressure was monitored noninvasively by a Finapres device (model 2300; Ohmeda, Trappes, France). The cuff size (small or medium) was adapted to the child's finger circumference, and the cuff was fitted to the third finger of the right hand, which was passively maintained at heart level during the study. The details of data sampling and analysis have been described previously.[19] The analog outputs of the Datex monitor and of the Finapres device were connected to an analog-to-digital converter to permit data acquisition, storage, and analysis using a microcomputer. BP and ECG signals were digitized (300 Hz) and processed by an algorithm based on feature extraction to detect and measure the characteristics of a BP cycle and an R wave (Acqknowledge v3.25; Biopac Systems, Inc.). SBP was extracted from the BP signal. A resampling rate of 10 Hz was chosen without interpolation, *i.e.*, SBP and HR values were replicated every 0.1 s until a new BP cycle or R wave occurred within a 0.1-s window. The evenly spaced sampling allowed direct spectral analysis using a fast Fourier transformed algorithm on a 512-point stationary time series. This corresponded to a period of 51.2 s at our sampling rate. Power of the HR or BP spectrum (ordinates) had units of $(beats/min)^2$ or $(mmHg)^2$ and was used for calculations and statistical analysis. The integration of the values of consecutive bands was computed to estimate the various components of the variability. The TSP was taken as the overall variability and was obtained by integration of all the spectral bands after exclusion of the first one. The LF component was obtained by integration of the values of six consecutive bands from 0.039 to 0.137 Hz of SBP or HR spectrum, to include the 10-s rhythm (0.1 Hz). The HF oscillation was obtained by integration of consecutive bands from 0.215 Hz to 0.703 Hz to include those corresponding to the spontaneous breathing rates of all children.

Statistical Analysis

Data of the three randomized groups ($Halo_{N_2O}$, $Sevo_{RAPID}$, and $Sevo_{INCR}$) were analyzed after logarithmic transformation using analysis of variance for repeated measures followed by Scheffé *post hoc* tests (Statview version 5.0; Abacus Concept, Inc., Berkeley, CA). Data of the additional group ($Sevo_{N_2O}$) were compared after log-

Table 1. Population Data

	$Halo_{N_2O}$	$Sevo_{INCR}$	$Sevo_{RAPID}$	$Sevo_{N_2O}$
Number of patients	13	11	11	10
Age (months)	57 ± 12	56 ± 11	65 ± 21	54 ± 27
Weight (kg)	18 ± 4	19 ± 5	21 ± 7	17 ± 6
Rectal midazolam (mg/kg)	0.5 ± 0.0	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1
Time to loss of eyelash reflex (s)	108 ± 34	81 ± 17***	61 ± 13***	62 ± 17†††
Expired concentration at loss of eyelash reflex (%)	2.2 ± 0.5	5.6 ± 0.7***	4.9 ± 0.7***	5.1 ± 0.8†††
Airway obstruction (%)	8	27	27	80††
Agitation (%)	54	91*	91*	60
Time to agitation (s)	84 ± 30	61 ± 19	58 ± 19*	53 ± 11†
Duration of agitation (s)	60 ± 36	63 ± 27	52 ± 29	45 ± 30
Time to central pupils (s)	338 ± 59	309 ± 36	304 ± 37	326 ± 81
Expired concentration at central pupils (%)	2.3 ± 0.4	5.5 ± 0.3***	5.2 ± 0.3***	5.5 ± 0.5†††
Expired concentration 5 min after intubation (%)	0.9 ± 0.1	2.6 ± 0.1***	2.6 ± 0.2***	2.7 ± 0.2†††

Data are mean ± SD.

Significant differences between $Halo_{N_2O}$, $Sevo_{RAPID}$, and $Sevo_{INCR}$ groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Significant differences between $Halo_{N_2O}$ and $Sevo_{N_2O}$ groups (†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$).

arithmic transformation to those of the halothane group using analysis of variance for repeated measures followed by Scheffé *post hoc* tests. The effects of switching halothane for sevoflurane on EEG parameters were studied using a paired *t* test (six patients). Nominal data were compared using the chi-square test. *P* values < 0.05 were considered significant. Data are expressed as mean ± SD.

Results

Thirteen children were enrolled in the halothane group, 11 in $Sevo_{INCR}$ and $Sevo_{RAPID}$ groups, and 10 in the additional group ($Sevo_{N_2O}$). The four groups were comparable with regard to age and weight (table 1). Loss of eyelash reflex occurred earlier in sevoflurane groups compared with the halothane group, but the time to obtain central pupils was not significantly different among the four groups. Most of the children required insertion of an oral airway within the first 3 min of induction to relieve partial airway obstruction. Airway obstruction was more frequently observed in the $Sevo_{N_2O}$ group compared with the other groups. The airways of one child in the $Halo_{N_2O}$ group and 3 of 11 in the $Sevo_{INCR}$ and $Sevo_{RAPID}$ groups remained partly obstructed during the early induction phase despite insertion of the oral airway. Oxygen saturation was maintained at $> 96\%$ throughout the study in all children. In the four groups, respiratory frequency increased significantly at loss of eyelash reflex compared with control awake values ($P < 0.001$). No hypercapnia (defined as end-tidal carbon dioxide > 48 mmHg) was observed in any group.

Transient agitation was observed in 7 of 13 children in the $Halo_{N_2O}$ group compared with 10 of 11 in the $Sevo_{INCR}$ and $Sevo_{RAPID}$ groups ($P = 0.04$). Incidence of agitation was not different between the $Halo_{N_2O}$ and $Sevo_{N_2O}$ groups. Uncoordinated movements occurred a few seconds before loss of eyelash reflex, were generalized (score 2), and lasted on average < 1 min. No clinical signs of seizure were observed in any group.

EEG Data Analysis

Complete EEG tracings were obtained in all patients; therefore, 45 recordings were analyzed. No seizure-like activity was recorded in any group. All calculated parameters changed significantly with time ($P < 0.001$). In the four groups, induction of anesthesia was associated with an increase in TSP and a shift toward the LF bands (table 2). At the time of loss of eyelash reflex, EEG patterns were different in sevoflurane groups compared with the halothane group: the slow waves (δ) were more prominent, whereas the fast rhythms (β) were less pronounced, as reflected by lower δ ratio and median power frequency during sevoflurane anesthesia compared with halothane. Spectral components were comparable during deep anesthesia (central pupils). During maintenance of anesthesia, 5 min after tracheal intubation, the differences between sevoflurane and halothane reappeared; the typical halothane tracing was composed of slow waves superimposed with fast rhythms ($\alpha + \beta$) similar to barbiturate spindles, whereas typical sevoflurane tracing contained mainly sharp slow waves with

Table 2. EEG Data

	Total Spectral Power (μV^2)	Median Power Frequency (Hz)	Spectral Edge 95 (Hz)	δ Ratio
Baseline				
$Halo_{N_2O}$	274 ± 70	6.6 ± 1.0	23.0 ± 1.3	1.2 ± 0.3
$Sevo_{INCR}$	253 ± 93	6.3 ± 1.3	22.7 ± 0.7	1.1 ± 0.3
$Sevo_{RAPID}$	212 ± 50	6.5 ± 1.7	22.4 ± 0.8	1.1 ± 0.3
$Sevo_{N_2O}$	290 ± 73	8.1 ± 2.6	24.3 ± 1.3†	1.4 ± 0.5
Loss of eyelash reflex				
$Halo_{N_2O}$	462 ± 282	6.4 ± 2.0	22.8 ± 1.8	1.1 ± 0.5
$Sevo_{INCR}$	700 ± 293*	3.4 ± 0.9***	18.6 ± 1.3***	0.5 ± 0.2***
$Sevo_{RAPID}$	555 ± 159	3.5 ± 1.1***	18.5 ± 1.5***	0.5 ± 0.3***
$Sevo_{N_2O}$	853 ± 292††	3.4 ± 0.9†††	20.3 ± 2.7††	0.5 ± 0.2†††
Central pupils				
$Halo_{N_2O}$	779 ± 172	4.1 ± 1.4	19.5 ± 2.4	0.6 ± 0.2
$Sevo_{INCR}$	918 ± 187	3.5 ± 0.6	19.6 ± 1.4	0.5 ± 0.1
$Sevo_{RAPID}$	875 ± 227	3.6 ± 0.5	19.5 ± 2.8	0.5 ± 0.1
$Sevo_{N_2O}$	1022 ± 247††	3.5 ± 0.6	20.0 ± 2.4	0.5 ± 0.2
5 min after intubation				
$Halo_{N_2O}$	635 ± 182	7.4 ± 1.7	20.1 ± 2.1	1.4 ± 0.6
$Sevo_{INCR}$	787 ± 149	3.4 ± 0.6***	19.8 ± 1.8	0.5 ± 0.1***
$Sevo_{RAPID}$	762 ± 173	3.5 ± 0.7***	19.0 ± 2.5	0.5 ± 0.1***
$Sevo_{N_2O}$	937 ± 181†††	3.5 ± 0.8†††	19.5 ± 1.4	0.5 ± 0.1†††

Data are mean ± SD.

Significant differences between $Halo_{N_2O}$, $Sevo_{RAPID}$, and $Sevo_{INCR}$ groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Significant differences between $Halo_{N_2O}$ and $Sevo_{N_2O}$ groups (†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$).

very few fast rhythms (fig. 1). TSP tended to be higher under sevoflurane compared with halothane, but this increase reached statistical significance only when N_2O was added in the additional group ($Sevo_{N_2O}$).

In 6 of the 13 patients induced with halothane, EEG was further recorded 5 min after switching halothane (0.9% ± 0.1% end tidal) for sevoflurane (2.5% ± 0.2% end tidal) for maintenance of anesthesia. In these 6 children, EEG tracings changed rapidly after sevoflurane was introduced: TSP increased, whereas median power frequency and δ ratio decreased significantly compared with halothane at similar MAC values ($P = 0.05$, $P = 0.001$, and $P < 0.001$, respectively; fig. 2).

Hemodynamic Data Analysis

Two patients were excluded for analysis of this part of the study: one in the $Halo_{N_2O}$ group for not obtaining accurate finger BP signal, and one in the $Sevo_{RAPID}$ group because baseline ECG showed supraventricular extrasystoles, thus preventing accurate spectral analysis. Therefore, 43 recordings of finger BP and HR were analyzed (12 in the $Halo_{N_2O}$ group, 11 in the $Sevo_{INCR}$ group, 10 in the $Sevo_{RAPID}$ group, and 10 in the $Sevo_{N_2O}$ group). Typical HR and SBP tracings and spectra are shown in fig. 3. All hemodynamic parameters (tables 3 and 4) changed significantly with time ($P < 0.001$).

Heart Rate. Mean level of HR was higher during induction of anesthesia with sevoflurane compared with halothane at all recorded times (table 3). No significant changes in HR were observed in the halothane group. In the sevoflurane groups, HR initially increased markedly, and maximal increase was, on average, 37 beats/min at loss of eyelash reflex. After this initial increase, HR decreased but remained higher than baseline values in the sevoflurane groups.

At baseline, children showed a high degree of HR variability as estimated by the TSP. Frequency domain analysis of this variability showed classical components, mainly assessed by the LF peak and the respiratory peak (HF) of the power spectra. In the four groups, induction of anesthesia was associated with a marked decrease in TSP, reflecting the loss of autonomic control on the sinus node. However, in sevoflurane groups, TSP and HF components were lower than in the halothane group. The LF/HF ratio increased at loss of eyelash reflex and 5 min after tracheal intubation with sevoflurane compared with halothane.

Arterial Pressure. Induction of anesthesia was associated with a comparable reduction in SBP in the four groups; this decrease in SBP was maximum before tracheal intubation (central pupils) and was equal to 24%,

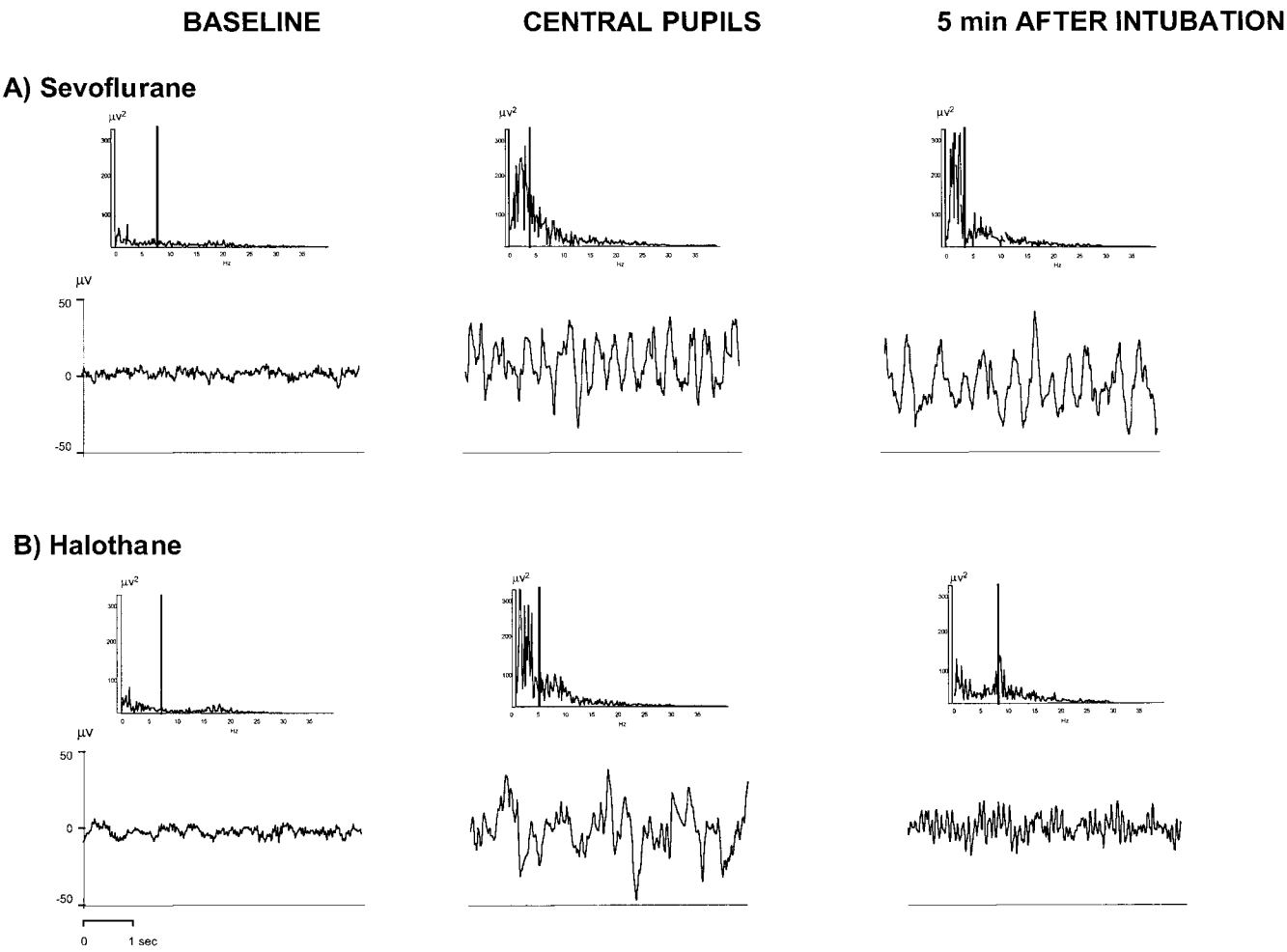

Fig. 1. Examples of electroencephalogram tracings recorded during induction of anesthesia with sevoflurane and halothane at baseline (*left*), at central pupils (*middle*), and 5 min after tracheal intubation (*right*) with the corresponding power spectra.

21%, 28%, and 34% in the $Halo_{N_2O}$, $Sevo_{INCR}$, $Sevo_{RAPID}$, and $Sevo_{N_2O}$ groups, respectively (table 4).

At baseline, all children showed a similar SBP spectral profile in which the LF component accounted for approximately 60% of the overall variability. As expected, TSP was markedly reduced in the four groups during anesthesia. Five minutes after intubation, SBP spectra showed mainly HF peaks, accounting for $>$ 80% of the overall variability and reflecting mechanical influence of controlled ventilation on SBP. These respiratory fluctuations were more pronounced in the two sevoflurane groups compared with the halothane group.

However, at loss of eyelash reflex, changes in SBP profiles were opposite: in the halothane group, the overall variability tended to decrease as expected with a reduction in LF component, whereas in sevoflurane groups, an increase in the overall variability associated with a increase of the LF component was observed.

Discussion

Sevoflurane induction was associated with frequent transient clinical agitation and rapid EEG changes different from those observed with halothane, but clinical or electrical seizure activity was not evidenced in these children premedicated with midazolam. During sevoflurane induction, cardiovascular changes were characterized by a marked inhibition of parasympathetic control of HR together with a transient relative increase in sympathetic vascular tone.

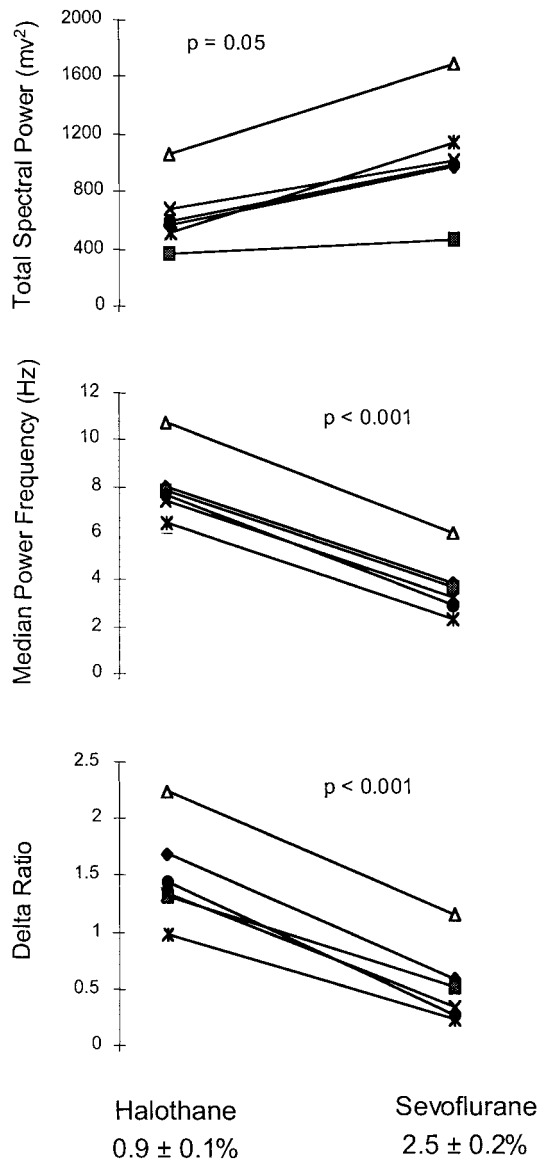

Fig. 2. Individual changes in electroencephalogram total spectral power, median power frequency, and δ ratio after switching halothane (0.9% ± 0.1% end tidal) for sevoflurane (2.5% ± 0.2% end tidal) in six children in the $Halo_{N_2O}$ group. *P* values are indicated (paired *t* test).

Clinical Data

Induction was more rapid with sevoflurane compared with halothane, especially when an initial high concentration of sevoflurane was used. These data are consistent with all previous reports.[3–5,29] Time to loss of eyelash reflex was longer than that previously reported using sevoflurane in a mixture of oxygen and nitrous oxide,[30,31] and this may be related to the high incidence of airway obstruction in this particular subgroup of patients, because most of the children had obstructive tonsils. Indeed, both halothane and sevoflurane are known to promote the collapse of the pharyngeal airway, leading to upper airway obstruction in children.‖ Transient agitation was more frequent when sevoflurane was administered with 100% O_2 compared with halothane or sevoflurane, both given in a mixture of oxygen and nitrous oxide. The addition of nitrous oxide seems to decrease the incidence of agitation during sevoflurane induction, as previously reported.[3,5] Agitation was usually observed at time of loss of consciousness and lasted, on average, 1 min, whatever the agent used. Agitation consisted mainly of uncoordinated movements, including hypertonia of the upper body together with bending of lower and upper limbs, but no clinical signs of seizure activity were observed. Agitation occurred at the time of hemodynamic changes.

EEG Study

Baseline EEGs were normal according to the children's age. Most tracings showed marked β activity predominantly in the frontal areas as a result from anesthetic premedication with midazolam.[32–34] No seizure-like activity was recorded on the EEG tracings. Because midazolam has antiepileptic activity and is used for emergency treatment of seizures,[35,36] the lack of evidence of seizure-like activity in our study may not apply to patients who are not premedicated. However, as previously mentioned, only case reports have described clinical seizure-like activity during induction or maintenance of anesthesia with high-dose sevoflurane[6–8] and EEG patterns of seizures in epileptic children,[9] although > 30 million patients had been anesthetized with sevoflurane by the end of 1998. EEG changes observed during halothane induction are consistent with those previously reported in adults and children.[37–42] Basically, halothane anesthesia is associated with an increase in EEG TSP with a shift from low-voltage fast waves to high-voltage slow waves, together with a relative increase in the production of 14–30-Hz activity. This later β activity is mainly composed of fast rhythms similar to barbiturate spindles and is observed at 1 MAC halothane, whereas it decreases with increasing halothane concentration.[43] The increase in δ power when end-tidal halothane concentration decreased from 2.3% ± 0.4% (just before tracheal

‖ Motoyama E, Maekawa N, Kamikawa K, Suzuki G, Obara H: Inspiratory muscle incoordination and upper airway obstruction in children during inhalational anesthesia (abstract). ANESTHESIOLOGY 1995; 83: A1187.

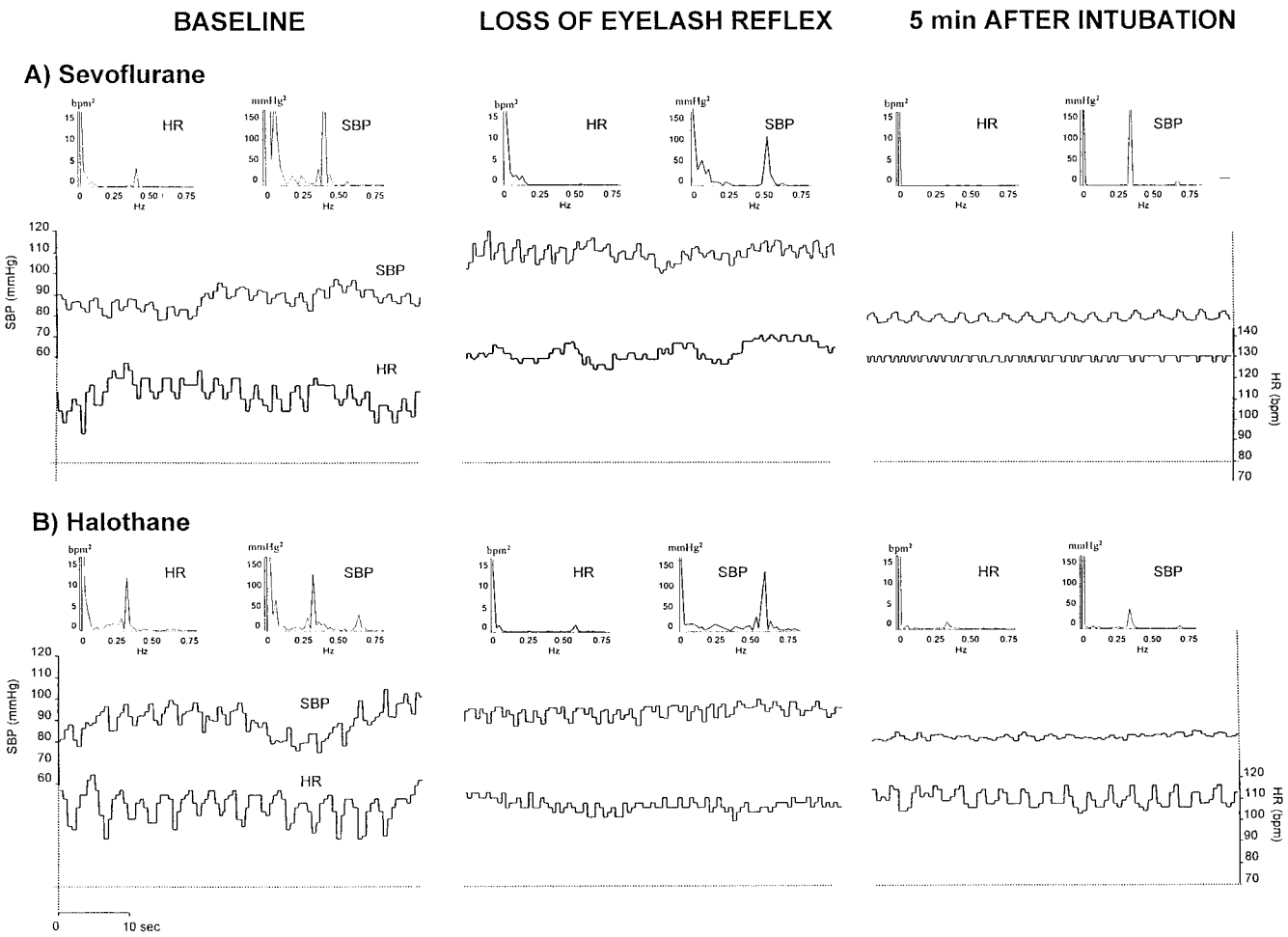

Fig. 3. Examples of systolic blood pressure (SBP) and heart rate (HR) tracings recorded during induction of anesthesia with sevoflurane and halothane at baseline (*left*), loss of eyelash reflex (*middle*), and 5 min after tracheal intubation (*right*) with the corresponding power spectra.

intubation) to 0.9% ± 0.1% (5 min after intubation) in our study reflects the changes in the proportion of fast rhythms with decreasing halothane concentration. Changes in α and β activity seem to be the most useful bands for monitoring depth of halothane anesthesia.[40] Conversely, during sevoflurane anesthesia, EEG changes are very similar with those observed with isoflurane or desflurane.[44] Median power frequency decreases, whereas TSP and relative power in the δ and θ bands increase, and power in the β band decreases.[44–46] No spindle-like activity can be evidence on the sevoflurane EEG tracings. At the three times of EEG analysis, tracings in the sevoflurane groups were very similar despite the fact that depth of anesthesia, as assessed by end-tidal anesthetic concentration, was different. This is in agreement with recent data that indicate that EEG parameters are useful indicators of depth of sedation with sevoflurane but bad predictors of movement after skin incision.[47] EEG profile during anesthesia maintenance with sevoflurane is different from the one observed with halothane, as demonstrated by EEG changes observed in the same children when switching from halothane to sevoflurane (fig. 2), whereas less differences are observed at deeper anesthesia. This might reflect differential effect of volatile anesthetics on brain activity or different states of anesthesia, because sevoflurane has a much lower blood/gas partition coefficient than that of halothane, resulting in a faster blood and tissue uptake. These differences between sevoflurane and halothane have been observed whether or not sevoflurane was administered in oxygen or in a mixture of oxygen and nitrous oxide. It is known that the addition of N_2O to a

Table 3. Heart Rate Data

	HR (beats/min)	Total Spectral Power (beats/min)^2	LF (beats/min)^2	HF (beats/min)^2	LF/HF
Baseline					
$Halo_{N_2O}$	100 ± 13	57.1 ± 36.9	32.1 ± 17.1	23.0 ± 23.9	2.7 ± 2.3
$Sevo_{INCR}$	103 ± 5	41.9 ± 31.3	25.0 ± 13.6	15.5 ± 19.0	2.3 ± 1.5
$Sevo_{RAPID}$	99 ± 21	78.5 ± 58.4	44.5 ± 42.0	30.0 ± 29.5	3.0 ± 4.5
$Sevo_{N_2O}$	105 ± 15	41.6 ± 29.3	26.1 ± 20.7	14.0 ± 9.5	2.3 ± 1.4
Loss of eyelash reflex					
$Halo_{N_2O}$	109 ± 18	21.1 ± 18.3	11.6 ± 9.2	8.4 ± 10.7	2.5 ± 2.5
$Sevo_{INCR}$	142 ± 14***	18.6 ± 17.0	15.7 ± 15.3	1.7 ± 1.1*	7.5 ± 4.3
$Sevo_{RAPID}$	136 ± 12**	9.0 ± 6.4	7.3 ± 6.6	1.2 ± 0.5**	7.6 ± 9.8
$Sevo_{N_2O}$	148 ± 18†††	9.6 ± 5.0	7.6 ± 4.7	1.1 ± 0.4††	6.6 ± 3.2††
Central pupils					
$Halo_{N_2O}$	94 ± 17	17.5 ± 18.4	8.6 ± 9.3	7.5 ± 8.6	1.7 ± 1.8
$Sevo_{INCR}$	121 ± 10**	3.7 ± 1.3*	1.8 ± 0.9	1.6 ± 0.9	1.5 ± 1.1
$Sevo_{RAPID}$	126 ± 18***	2.7 ± 1.5**	1.1 ± 1.1**	1.2 ± 0.5*	0.9 ± 0.6**
$Sevo_{N_2O}$	115 ± 22†	7.6 ± 10.5	1.8 ± 1.9†	4.2 ± 5.5	0.7 ± 0.6†
5 min after intubation					
$Halo_{N_2O}$	95 ± 10	5.8 ± 4.2	1.0 ± 0.6	4.0 ± 3.2	0.4 ± 0.2
$Sevo_{INCR}$	118 ± 11***	1.2 ± 0.4***	0.3 ± 0.2**	0.4 ± 0.2***	1.1 ± 0.8**
$Sevo_{RAPID}$	119 ± 20***	1.4 ± 0.6***	0.5 ± 0.3*	0.4 ± 0.2***	1.7 ± 1.4*
$Sevo_{N_2O}$	118 ± 23††	1.1 ± 0.4†††	0.2 ± 0.2†††	0.7 ± 0.2†††	0.3 ± 0.3

Data are mean ± SD.

Significant differences between $Halo_{N_2O}$, $Sevo_{RAPID}$, and $Sevo_{INCR}$ groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Significant differences between $Halo_{N_2O}$ and $Sevo_{N_2O}$ groups (†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$).

HF = high frequency; HR = heart rate; LF = low frequency.

steady-state concentration of halothane or isoflurane decreases TSP and α- and β-range EEG power, whereas δ- and θ-range power increases.[41] These changes may be different during anesthesia induction because steady state is not achieved.

Hemodynamic Study

Heart Rate Profiles. Heart rate was basically unchanged during halothane induction, whereas it increased significantly in the sevoflurane groups. This increase was maximal at the time of loss of eyelash reflex. No differences in HR variability and profiles were observed between groups at baseline. All children were premedicated with midazolam. Midazolam decreases spectral components of HR variability but does not change the LF/HF ratio.[48] Most anesthetic agents induce a dose-dependent inhibition of cardiac autonomic control, leading to a noticeable reduction of spontaneous fluctuations of HR.[49–51] In the four groups, the decrease of overall HR variability during induction, as assessed by the TSP, is consistent with this autonomic inhibition. However, HR profiles during induction of anesthesia differed markedly between the sevoflurane groups and the halothane group. This has also been described by other investigators.[52] Halothane anesthesia induces a decrease in LF and HF powers, suggesting that this agent alters both sympathetic and parasympathetic HR control. However, the respiratory-related parasympathetic modulation of HR seems to be relatively more preserved during halothane anesthesia compared with sevoflurane as assessed by the lower HF spectral powers. The relative preservation of vagal tone during halothane anesthesia has been previously reported in infants.[49] Basically, induction with sevoflurane is associated with an abrupt increase in HR occurring around the time of loss of eyelash reflex. This marked HR acceleration is associated with a disappearance of respiratory sinus arrhythmia, assessed by HF fluctuations, which are primarily mediated by the parasympathetic system. Our results suggest that this early increase in HR, described in children,[3,16] might result from a withdrawal of parasympathetic cardiac activity. In healthy adult volunteers who were not premedicated, administration of sevoflurane in doses ranging from 0.4 to 1.2 MAC was associated with stable HR without transient acceleration.[17,53,54] This discrepancy between adult data and our present findings may result from the high level of parasympathetic tone observed in healthy children responsible for large vagally mediated respiratory sinus arrhythmia. Cardiac autonomic inhibition (sympathetic and parasympathetic)

Table 4. Systolic Blood Pressure Data

	SBP (mmHg)	Total Spectral Power $(mmHg)^2$	LF $(mmHg)^2$	HF $(mmHg)^2$	LF/HF
Baseline					
$Halo_{N_2O}$	97 ± 15	23.7 ± 14.2	15.6 ± 10.0	7.7 ± 5.0	2.6 ± 1.9
$Sevo_{INCR}$	90 ± 14	19.8 ± 13.9	13.0 ± 8.7	6.3 ± 7.7	3.9 ± 4.4
$Sevo_{RAPID}$	93 ± 13	22.8 ± 22.6	15.2 ± 16.5	7.5 ± 8.1	2.5 ± 1.6
$Sevo_{N_2O}$	95 ± 11	14.4 ± 18.2†	7.2 ± 4.1†	7.9 ± 14.6	2.4 ± 2.0
Loss of eyelash reflex					
$Halo_{N_2O}$	91 ± 16	16.9 ± 10.1	8.0 ± 5.6	7.4 ± 4.8	1.3 ± 0.8
$Sevo_{INCR}$	99 ± 22	35.1 ± 23.0*	21.3 ± 13.8*	12.7 ± 9.5	1.8 ± 0.7
$Sevo_{RAPID}$	96 ± 15	37.6 ± 16.3*	18.8 ± 12.2*	17.2 ± 11.8*	1.9 ± 1.9
$Sevo_{N_2O}$	102 ± 11	47.3 ± 33.9††	21.6 ± 20.9†	24.0 ± 19.2††	1.0 ± 0.8
Central pupils					
$Halo_{N_2O}$	73 ± 14	4.3 ± 2.3	2.4 ± 1.1	1.7 ± 2.0	2.7 ± 2.4
$Sevo_{INCR}$	71 ± 23	4.7 ± 4.9	2.1 ± 2.3	2.5 ± 2.7	1.2 ± 1.1
$Sevo_{RAPID}$	68 ± 12	3.6 ± 1.4	1.3 ± 1.1*	2.1 ± 1.3	1.1 ± 1.5*
$Sevo_{N_2O}$	63 ± 12	4.5 ± 4.7	0.8 ± 0.5†††	2.7 ± 3.4	0.6 ± 0.5†††
5 min after intubation					
$Halo_{N_2O}$	79 ± 13	1.0 ± 0.7	0.2 ± 0.1	0.7 ± 0.6	0.4 ± 0.4
$Sevo_{INCR}$	81 ± 15	2.8 ± 2.2**	0.2 ± 0.3	2.3 ± 1.8***	0.1 ± 0.1**
$Sevo_{RAPID}$	73 ± 8	1.6 ± 0.6	0.1 ± 0.1	1.3 ± 0.6*	0.1 ± 0.1**
$Sevo_{N_2O}$	75 ± 6	1.4 ± 1.2	0.1 ± 0.1	1.2 ± 1.1	0.2 ± 0.2†

Data are mean ± SD.

Significant differences between $Halo_{N_2O}$, $Sevo_{RAPID}$, and $Sevo_{INCR}$ groups (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

Significant differences between $Halo_{N_2O}$ and $Sevo_{N_2O}$ groups (†$P < 0.05$; ††$P < 0.01$; †††$P < 0.001$).

HF = high frequency; HR = heart rate; LF = low frequency.

seems to be more profound with sevoflurane than with halothane, as evidenced by the lower LF and HF powers during maintenance of anesthesia.

Systolic Blood Pressure Profiles. Both halothane and sevoflurane induce an identical decrease in BP during induction of anesthesia. However, this decrease results from different mechanisms: both agents alter myocardial contractility, but the effects of sevoflurane are less pronounced than those of halothane, and sevoflurane decreases peripheral vascular resistances, whereas the latter remain unchanged with halothane.[1,2] As expected, at baseline, overall variability of SBP was mainly caused by LF oscillations. However, respiratory fluctuations were important during spontaneous ventilation in all children, probably reflecting inspiratory efforts as a result of partial airway obstruction in premedicated children with hypertrophic tonsils. During anesthesia, a large decrease of the LF component was evidenced, reflecting a noticeable reduction of the nervous sympathetic activity. Sympathetic inhibition induced by general anesthetics has been extensively studied in human using a microneurographic technique.[17,55] In healthy adult volunteers, sevoflurane seems to preserve nervous sympathetic traffic when up to 1.2 MAC is administered. However, in our study, sympathetic inhibition was observed at the time of tracheal intubation and was still present 5 min later when expired sevoflurane concentration was close to 1 MAC. The magnitude of respiratory SBP fluctuations is related to effective blood volume.[56] The mechanical influence of standardized controlled ventilation on SBP was more pronounced in the two sevoflurane groups than in the halothane group despite unchanged blood volume, suggesting that vascular tonus was lower with sevoflurane compared with halothane. This is consistent with a more potent vasodilatatory effect of sevoflurane compared with halothane.[1]

An interesting finding is the SBP spectral differences between halothane and sevoflurane evidenced at the time of loss of eyelash reflex. In the halothane group, spectral profile of SBP was between awakening and deep-anesthesia profiles, reflecting progressive autonomic depression. Conversely, in the sevoflurane groups, spectral profile of SBP calculated at the time of loss of eyelash reflex showed a pattern close to that calculated at baseline. Moreover, overall variability (TSP), LF power, and HF power tended to increase compared with baseline, even if this increase reached statistical significance only when nitrous oxide was added. Although sympathetic activation has been demonstrated with desflurane or isoflurane,[17,55,57] most stud-

ies have failed to demonstrate the same process with sevoflurane. However, an increase of norepinephrine during rapid induction with sevoflurane in a mixture of oxygen/nitrous oxide has been reported before tracheal intubation.[58] Our results suggest that at loss of eyelash reflex, vascular nervous sympathetic activity may be maintained or increased with sevoflurane even in premedicated subjects.

Conclusion

Induction of anesthesia with halothane or sevoflurane is associated with marked changes in EEG activity and HR and SBP profiles in children. Agitation observed at the time of loss of eyelash reflex is more frequent when sevoflurane is administered with 100% O_2 compared with halothane or sevoflurane given in a mixture of nitrous oxide and oxygen. Agitation frequently observed during sevoflurane induction in our study was not associated with clinical or electrical seizure activity in children premedicated with midazolam. Except at a deep level of anesthesia, EEG profiles are different with the two agents; halothane tracings are composed of slow waves superimposed with spindles, whereas sevoflurane tracings mainly consist of sharp, slow waves. Sevoflurane markedly inhibits the parasympathetic control of HR and increases relatively transiently sympathetic vascular tone. This helps to explain the transient increase in HR and SBP often observed in children in the early induction phase.

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